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5. évfolyam · 8. szám · 1995. augusztus

IMPAKT

TÉNYEK A TUDOMÁNYOS ALAPKUTATÁSRÓL

Szilárd: **Csak a tényeket írom le – nem azért, hogy bárki is elolvassa, csakis a Jóisten számára.**
Bethe: **Nem gondolod, hogy a Jóisten ismeri a tényeket?**
Szilárd: **Lehet, hogy ismeri, de a tényeknek nem *ezt* a változatát.**

[*Leo Szilard, His version of the Facts. S.R. Weart & Gertrud Weiss Szilard* (Eds), MIT Press, Cambridge, MA, 1978, p.149.]

A tartalomból:

ISSN 1215-3702

America's Best Research University? Stanford Soars in Top Ten Tournament

Which U.S. universities perform best in scientific research? The old-line institutions or younger, hungrier universities striving to make a mark? Public or private institutions? Big, research-intensive universities active across the entire spectrum of science or smaller schools that choose to focus on a few areas? There are, of course, many ways to gauge success in research. *Science Watch* relies primarily on citation measures that reveal the extent to which the scientific community as a whole draws upon research in a particular field conducted at specific universities.

Using exclusive publication and citation data on over 100 U.S. universities from ISI's *University Science Indicators on Diskette* database, *Science Watch*, presents a two-part series on the ten highest-impact universities in each of 21 fields for the period 1981-1993. Nine rankings in the biological sciences appear in this issue. Additional listings, covering the physical sciences and a few fields in the social sciences, will appear later.

Science Watch assessed a research performance over the last 13 years based on the citation impact of papers published in ISI-indexed journals. Citation impact is citations per paper, a weighted measure that allows smaller producers of papers to complete fairly against larger universities that turn out reams of research reports. Nevertheless, in each ranking, *Science Watch* did set a minimum threshold for number of papers produced during the 13-year period. This threshold varied from field to field in order to reflect the differing size of the journal literature that defined each field and the population of researchers within each respective discipline. The more numerous the journals and researchers within a field, of course, the more papers and citations generated.

Highest-Impact U.S. Universities 1981-93
(Ranked by frequency of Top Ten appearances in 21 fields)

Rank	Institution	Top Ten Appearances
1	Stanford University	17
2	Harvard University	13
3	Yale University	13
4	MIT	12
5	Caltech	9
6	Univ. Calif., Berkeley	9
7	University of Chicago	8
8	Cornell University	8
9	Princeton University	6
10	University of Washington	6

Science Watch then examined the citation-per-paper score of each university, comparing that mark to the world average for the field. In clinical medicine, for example, Stanford's citations-per-paper score for papers published and cited during the period of 1981-93 was 21.82. The world average was 11.29. Thus, Stanford scored 93% higher than the world average, while second-ranked Harvard's papers earned 86% more citation per paper than the world average, and so on.

(More tables and commentary follow on next pages)

MAGYAR TUDOMÁNYOS AKADÉMIA KÖNYVTÁRA

Top Ten Universities in Biological Science Fields, 1981-93

Clinical Medicine
>1,000 papers

Rank	Institution	# of Papers	Relative Impact
1	Stanford University	3,745	+93
2	Harvard University	11,855	+86
3	University of Washington	5,034	+84
4	Univ. Calif., San Francisco	6,988	+80
5	Boston University	2,286	+80
6	Tufts University	1,826	+80
7	Cornell University	2,853	+78
8	University of Minnesota	4,603	+61
9	Univ. Calif., Los Angeles	7,318	+57
10	Yale University	3,578	+53

Neuroscience
>500 papers

Rank	Institution	# of Papers	Relative Impact
1	Washington University	1,869	+109
2	Yale University	2,531	+85
3	Johns Hopkins University	2,546	+73
4	Stanford University	1,842	+72
5	MIT	812	+69
6	Cornell University	1,963	68
7	University of Chicago	1,374	+63
8	Harvard University	3,872	+62
9	Univ. Calif., Irvine	1,558	+60
10	Rockefeller University	1,113	+58

Molecular Biology & Genetics
>500 papers

Rank	Institution	# of Papers	Relative Impact
1	MIT	1,772	+246
2	Rockefeller University	1,246	+211
3	Harvard University	4,766	+172
4	Caltech	824	+172
5	Univ. Calif., San Francisco	2,464	+154
6	Princeton University	556	+141
7	Univ. Calif., San Diego	1,733	+139
8	Stanford University	2,333	+130
9	Univ. Texas, Southwest Med. Ctr., Dallas	845	+120
10	Univ. Calif., Berkeley	2,119	+119

Immunology
>500 papers

Rank	Institution	# of Papers	Relative Impact
1	Tufts University	669	+123
2	Stanford University	1,220	+90
3	Harvard University	3,385	+89
4	University of Colorado	737	+86
5	Yale University	697	+74
6	University of Chicago	516	+64
7	University of Washington	1,370	+61
8	Univ. Texas, Southwest Med. Ctr., Dallas	935	+50
9	Univ. Calif., San Francisco	1,013	+47
10	University of Alabama	918	+47

Plant & Animal Science
>500 papers

Rank	Institution	# of Papers	Relative Impact
1	Univ. Calif., San Diego	1,380	+195
2	Yale University	716	+133
3	SUNY Stony Brook	700	+132
4	Univ. Calif., Santa Barbara	761	+130
5	University of Washington	2,284	+116
6	Univ. Calif., Los Angeles	1,112	+116
7	Florida State University	670	+101
8	University of North Carolina	609	+100
9	Indiana University	531	+94
10	University of Colorado	732	+93

Pharmacology
>500 papers

Rank	Institution	# of Papers	Relative Impact
1	Stanford University	516	+124
2	Univ. Calif., San Diego	523	+121
3	University of Colorado	550	+115
4	Johns Hopkins University	724	+109
5	Vanderbilt University	727	+100
6	Yale University	606	+99
7	Duke University	760	+97
8	University of Arizona	1,028	+77
9	Univ. Calif., San Francisco	1,220	+73
10	University of Michigan	1,192	+53

Agricultural Sciences
>1000 papers

Rank	Institution	# of Papers	Relative Impact
1	Univ. Wisconsin, Madison	1,903	+105
2	Cornell University	2,204	+98
3	University of Minnesota	1,830	+68
4	Univ. Illinois, Urbana	1,831	+67
5	Univ. Calif., Davis	2,234	60
6	N. Carolina State University	1,365	+51
7	Iowa State University	1,457	+44
8	Purdue University	1,243	+43
9	Michigan State University	1,189	+41
10	Pennsylvania State Univ.	1,000	+40

Biology & Biochemistry
>1000 papers

Rank	Institution	# of Papers	Relative Impact
1	Rockefeller University	2,136	+161
2	Univ. Texas, Southwest Med. Ctr., Dallas	4,010	+102
3	Vanderbilt University	3,727	+100
4	Harvard University	14,601	96
5	MIT	3,182	+94
6	Washington University	5,630	+93
7	Yale University	5,616	+93
8	University of Washington	6,479	89
9	Caltech	1,040	+89
10	Stanford University	4,665	+86

SOURCE: ISI's University Science Indicators on Diskette, 1981-93.

Ecology/Environment
>250 papers

Rank	Institution	# of Papers	Relative Impact
1	Univ. Calif., Santa Barbara	286	+185
2	Stanford University	464	+183
3	Duke University	541	+126
4	Michigan State University	615	+124
5	University of Washington	870	+117
6	Univ. Calif., Riverside	915	+113
7	Cornell University	1,263	+103
8	MIT	328	+98
9	University of Virginia	281	+95
10	University of Michigan	699	+94

Stanford, as the first table indicates, placed in the top ten in 17 out of 21 rankings — the best showing of any university. (Ties were broken by summing the ranks of each institutions: those with lower sum earned a higher place in the table on page 1).

Harvard, Yale, and MIT each placed in more than half of the top-ten rankings.

Viewed in another way, these top ten of the top-ten listings can be reranked by their average showings, calculated as the sum of their ranks divided by their number of appearances. By this measure, Harvard came out on top with a score of 2.85, followed by Stanford with 3.82. Princeton and the University of Chicago are next with 4.50 each, followed by MIT (4.75) and Yale (5.15), while Caltech (5.44), the University of Washington (5.83), Cornell (6.50) and the University of California, Berkeley (7.67) line up behind.

Science Watch 5(9):1-2, October 1994

China Tightens Appraisal System

China has adopted a new system to evaluate scientific and technical achievements that is expected to reduce cronyism, improve the quality of the reviews, and give more weight to market forces in judging the commercial value of new technologies. The new procedures, enacted earlier this year by the State Science and Technology Commission (SSTC) and hailed by scientists, also give scientific journals, through their publication decisions, a larger role in determining what basic research is worthy of continued funding.

The key changes involve the operation of appraisal committees, which for decades have shaped the professional lives of Chinese scientists. Any work tied to a governemnt plan — and in a socialist economy that has meant practically everything — had to be judged by a committee of half a dozen or so scientific experts, assembled by the relevant government body. Researchers could nominate their own reviewers, and it was not uncommon for prominent scientists to perform as many as 30 to 50 such appraisals a year. The reviews were intended to help the government decide what to fund, and the results also influenced salaries, promotions, and even housing allocations.

The system was also supposed to provide a seal of approval for technical achievements before they were put to use or offered to the public. Although China maintains a separate system for approval of new drugs and medical devices, a positive

(Continued on next page)

appraisal was something that companies could put into their advertising as additional proof of the quality of their product. In practice, however, it often produced exactly the opposite effect: Shoddy goods flooded the market accompanied by wildly inflated claims of efficacy, as appraisers were either too busy or too afraid of offending powerful colleagues to exercise proper scrutiny over the quality of the work.

In one case reported last year by government-run *Science and Technology Daily*, a device to measure the sulfur dioxide content of industrial emissions, funded by the Chongqing Environmental Protection Bureau at a cost of $3.4 million, passed its expert appraisal but nevertheless failed to perform. The problem, according to the news account, was that an appraisal committee at the Nanjing Chemical Industry Research Institute used pure sulfur dioxide rather than actual boiler smoke to test the device. A report based on these meaningless results was sent to the environmental agency, and, despite the absence of signatures from any committee members, the device was approved.

China's market for health care products and medicines has been especially vulnerable to exaggerated, if not fraudulent, claims. Glowing appraisal reports have routinely been touted in advertisements in Chinese media for a wide range of bizarre concoctions and devices such as hair-growth preparations, health tonics, and herbal "health belts."

The new system is expected to reduce the number of appraisals, substituting "market competition and academic exchanges," explained Han Deqian, vice chair of the SSTC, at a Beijing press conference. He estimated that the number of appraisals conducted nationwide — 33,000 last year — would drop by as much as 60%. Basic, theoretical, and social science research would not longer be required to undergo appraisals, he added, but appraisals will still be done in areas where, Han noted, "market mechanisms are not fully developed." For the rest, government agencies will accept the verdicts of journal editors as an objective measure of the quality of the research.

Officials at the SSTC say they hope that the changes, which also prohibit scientists from selecting their own appraisers and end mail reviews, will help end the endemic bribery and cronyism that plagued the old system. One prominent chemist at a Beijing research institute, who requested anonymity, says this widespread practice has become a major irritant for scientists. "It is very troubling when an old classmate or a close friend nominates you to appraise his research," he says. "You do not want to ruin a relationship by saying it is bad, but you cannot violate your integrity as a scientist by saying it is good when you know it really isn't." The only way out of this dilemma, he adds, is to file an appraisal that neither praises nor condemns the work.

Such ambiguous and anonymous appraisals were common under the old system. But the new rules make appraisers accountable for the verdicts they render. The consequences for knowingly giving a stamp of approval to substandard work will range from demotion to legal liability for resulting damages or losses.

Other changes in the procedures are expected to make the appraisals more rigorous. These include the requirement that scientists submitting research results for appraisal submit lab records. The SSTC says that a lighter workload should also allow appraisers to examine materials more critically, and thus, render more accurate judgments.

The changes has been well received by scientists, who believe it was long overdue. "Most working scientists believe the whole appraisal system is nonsense," says one Shanghai-based physicist. "If you've got results, then you go ahead and commercialize them. If it sells in the marketplace, that means it's good work. If it doesn't, that means it isn't," he said.

Ted Plakfer (free-lance writer in Beijing), Science, 268:23-24 (7 April 1995)

Immunology Research

Immunology has been a particularly active and visible field in these pages in recent years. Three years ago, this publication ranked the top 50 U.S. universities in immunology research according to citation impact (see *Science Watch*, 3[1]:7, January 1992.). For an update, *Science Watch* has identified 1,500 of the most-cited immunology papers published over the last five years in 67 ISI-indexed immunology journals, as well as immunology papers published in *Science*, *Nature*, and *Proceedings of the National Academy of Sciences of the United States of America*.

Using ISI's High Impact Papers in Immunology database, *Science Watch* examined the 300 most-cited papers of each year from 1990 to 1994. From this select group, the 25 most highly cited institutions and authors were identified and ranked — both by total citations (a measure that often reflects output) and by impact (citations per paper). Institutions appear in the table on the next page; authors are listed at page 6.

Papers by Harvard University researchers collected the highest number of total citations, while the University of Colorado grabbed the top spot in the citations-per-paper ranking. Harvard and Colorado, in fact, placed among the top ten on both lists, as did Stanford University and the National Jewish Center for Immunology and Respiratory Medicine, Denver.

In examining only the top ranks of the most-cited papers in immunology over the last five years, *Science Watch* cast a somewhat smaller net than usual. The resulting catch, however, was abundant: in each year, those 300 papers managed to pull in a substantial proportion of all citations in the field. In 1990, for example, the top 300 papers — just 2.7% of the more than 11,000 immunology papers in ISI-indexed journals that year — accounted for over 27% of all citations to immunology papers recorded from 1990 to 1994. As the accompanying graph shows, this percentage remained fairly consistent over the last 14 years — with the 300 most-cited papers collecting a quarter to one-third of all citations to immunology papers in each year.

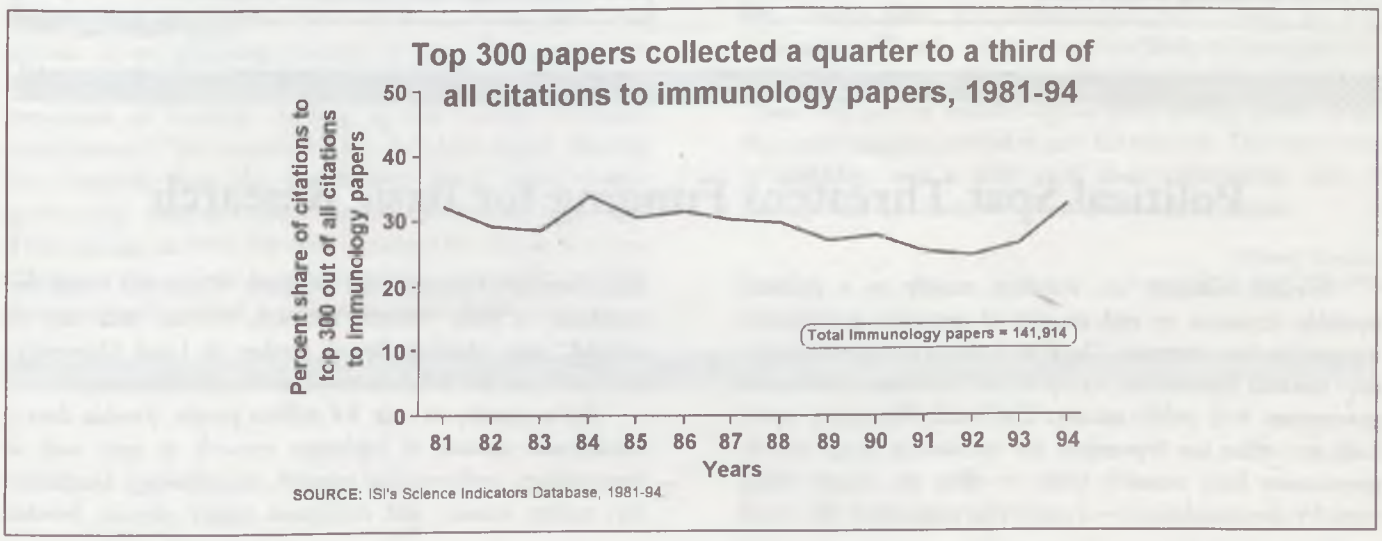
(Continued on next two pages)

Institutions Ranked by Citations and Citation Impact

(among those publishing ≥ 10 high-impact papers, 1990-94)

Rank	Institution	Citations 1990-94
1	Harvard University	14,956
2	NIH, NCI	8,171
3	NIH, NIAID	6,886
4	Stanford University	6,804
5	DNAX	4,849
6	University of Colorado	4,548
7	Natl. Jewish Ctr. Immunol.	4,243
8	University of Washington	3,988
9	Univ. California, San Francisco	3,733
10	Washington University	3,413
11	Brigham & Women's Hospital	3,111
12	University of Oxford	2,848
13	Scripps Clin. & Res. Fdn.	2,666
14	Yale University	2,246
15	Duke University	2,221
16	Genentech	1,838
17	University of Michigan	1,779
18	NIH, NICHHD	1,755
19	Osaka University	1,696
20	Institut Pasteur	1,672
21	Univ. Calif., Los Angeles	1,649
22	Immunex	1,639
23	Yeshiva Univ.- A. Einstein Coll.	1,597
24	Rockefeller University	1,567
25	Univ. Calif., San Diego	1,567

Rank	Institution	Citations 1990-94
1	University of Colorado	181.9
2	NIH, NICHHD	159.6
3	Natl. Jewish Ctr. Immunol.	151.5
4	Yeshiva Univ.- A. Einstein Coll.	133.1
5	University of Tokyo	112.1
6	Harvard University	108.4
7	Stanford University	100.1
8	Scripps Clin. & Res. Fdn.	98.7
9	Repligen Corp.	98.6
10	Rockefeller University	97.9
11	Genentech	96.7
12	DNAX	93.3
13	Duke University	92.5
14	University of Florence	91.8
15	Max Planck Inst. Biology	91.5
16	Ludwig Inst. Cancer Research	91.1
17	NIH, NCI	90.8
18	Osaka University	89.3
19	Uniformed Serv. Hlth. Sci. Univ.	89.2
20	University of Washington	88.6
21	Massachusetts General Hospital	88.4
22	Univ. Calif., San Diego	87.1
23	University of Oxford	86.3
24	Univ. California, San Francisco	84.8
25	University of Birmingham	84.8



Highly Cited Authors in Immunology, 1990-94

Ranked by Citations and Impact

(among those publishing ≥5 high-impact papers)

Rank	Name	Institution	Number of Papers	Total Citations
1	T.A. Springer	Harvard University	7	2,801
2	T.R. Mosmann	HHMI*, Univ. of Alberta	16	2,509
3	P. Marrack	HHMI, Natl. Jewish Ctr.	10	2,385
4	J.W. Kappler	HHMI, Natl. Jewish Ctr.	9	2,381
5	J.A. Ledbetter	Bristol-Myers Squibb	16	1,966
6	S. Shaw	NIH, NCI	12	1,788
7	D.F. Fiorentino	DNAX	10	1,754
8	Y. Shimizu	University of Michigan	9	1,616
9	R.C. Thompson	Synergen Inc.	5	1,572
10	K.W. Moore	DNAX	10	1,544
11	J.L. Strominger	Harvard University	15	1,474
12	A. Ogarra	DNAX	12	1,359
13	G.A. van Seventer	NIH, NCI	7	1,355
14	P.S. Linsley	Bristol-Myers Squibb	12	1,320
15	E.A. Clark	University of Washington	12	1,229
16	P. Cresswell	HHMI, Yale University	13	1,198
17	K.J. Morgan	MIH, NCI	6	1,171
18	A. Sher	NIH, NIAID	17	1,165
19	G.R. Crabtree	HHMI, Stanford University	5	1,123
20	P. Vieira	DNAX	6	1,114
21	S. Romagnani	University of Florence	12	1,102
22	T. Kishimoto	Osaka University	11	1,090
23	A.S. Fauci	NIH, NIAID	12	1,071
24	R.D. Klausner	NIH, NICHHD	7	1,049
25	C.A. Janeway	HHMI, Yale University	11	1,003

*** HHMI International Research Scholar**

Rank	Name	Institution	Number of Papers	Total Citations
1	T.A. Springer	Harvard University	7	400.1
2	R.C. Thompson	Synergen Inc.	5	314.4
3	J.W. Kappler	HHMI, Natl. Jewish Ctr.	9	264.6
4	P. Marrack	HHMI, Natl. Jewish Ctr.	10	238.5
5	G.R. Crabtree	HHMI, Stanford University	5	224.6
6	K.J. Morgan	MIH, NCI	6	195.2
7	G.A. van Seventer	NIH, NCI	7	193.6
8	P. Vieira	DNAX	6	185.7
9	S.D. Putney	Repligen Corp.	5	184.2
10	Y. Shimizu	University of Michigan	9	179.6
11	D.F. Fiorentino	DNAX	10	175.4
12	T. Hirano	Osaka University	5	167.8
13	J.C. Gorga	Harvard University	5	162.0
14	R.J. Ulevitch	Scripps Clin. & Res. Fdn.	5	160.6
15	E.C. Butcher	Stanford University	6	160.5
16	A. Townsend	HHMI*, University of Oxford	6	160.2
17	T.R. Mosmann	HHMI*, University of Alberta	16	156.8
18	K.W. Moore	DNAX	10	154.4
19	A.J. Langlois	Duke University	5	154.0
20	C.H. June	USN, Med. Res. Inst.	6	152.0
21	R.D. Klausner	NIH, NICHHD	7	149.9
22	S. Shaw	NIH, NCI	12	149.0
23	B.R. Bloom	HHMI, Yeshiva Univ.	5	147.4
24	E. Palmer	Natl. Jewish Ctr.	5	143.6
25	C.A. Dinarello	Tufts University	5	139.8

SOURCE: ISI's High Impact Papers in immunology, 1990-94.

Science Watch 6 (May 1995) 1

Political Spat Threatens Funding for Basic Research

Swedish scientists are watching tensely as a political squabble threatens to end decades of generous government support for basic research. The row is over a group of independent research foundations set up by the previous conservative government with public money. The Social Democrats, voted back into office last September, are considering savage cuts in government basic research funds to offset the money being spent by the foundations — a move that researchers fear could blunt Sweden's scientific edge for good. "Once you break the backbone of your research network, it's not that easy to rebuild," says physicist Ingolf Lindau of Lund University, director of the MAX-Lab national accelerator laboratory.

For a country of only 8.8 million people, Sweden does a considerable amount of big-league research, in areas such as immunology, cardiovascular research, microbiology, biochemistry, surface science, and condensed matter physics. Sweden

maintains its high-quality science by spending more than 3% of its national income — about $6 billion — on research and development. Per capita, that is more than any country except the United States and France, according to 1991 figures from the Organization for Economic Cooperation and Development. This largesse has made life pretty easy for Sweden's basic researchers, who generally receive adequate support from government research councils to do whatever interest them without being obliged to account for every penny — or even to use their grants for the projects described in their applications.

But that carefree state — the envy of scientists in other countries — is in jeopardy. The problem is a political tussle over $2.6 billion that Swedish corporations paid into a fund established by the socialist government in the early 1980s to help employees buy out their companies. When the conservatives took office in 1991, one of their campaign promises was to abolish this "Wage Earner Fund." After much debate and despite strong Socialist opposition, they dissolved the fund in 1993.

The conservatives used the capital to establish several foundations that will distribute $200 million worth of grants each year for strategic research to help Swedish industry to compete internationally. The foundations were made independent of government control so that their funding decisions would not be influenced by politics, says Per Unckel, who played a key role in their creation as minister of education in the conservative government (*Science*, 12 March 1993, p. 1536).

But this boon for applied scientists may have dire consequences for their colleagues in basic research. After the Social Democrats won last September's election, Carl Tham, the new education minister, began a personal crusade to either dissolve the research foundations or bring them under government control. Unckel says the conservatives worked hard to make them legally watertight, and so far, Tham has been unable to touch them. And in January, the foundations turned down Tham's formal request for a government say in their affairs.

Although he can't control the foundations, Tham does have power over his own department's budget. "If we can't dissolve these foundations, then we have to take them into account in our planning," he told *Science*. "That money was stolen from the public purse. We can't afford such an enormous expansion of research funding in the present economic environment." To compensate for the extra money flowing into research from the foundations, Tham wants to cut government research council funding by 50%, or more than $100 million, in 1997. He first broached the threat in a pre-Christmas letter to the foundations and is expected to confirm it in an official proposal to parliament on 27 April.

Tham asked the foundations to work together with the research councils to make up for any cuts in government funding. They turned him down, because their charters specify the types of projects they can support, and they don't have the flexibility to simply jump into the breach even if they wanted to.

All government departments are under pressure to cut their budgets, so Tham can easily justify his actions on strictly fiscal grounds. The national debt stands at $178 billion, and government expenditure outstripped revenue by almost 50% in December's figures. But Unckel says targeting the government's basic research investment could force Sweden's most gifted scientists to take better offers in other countries. "Tham is a fool," he says. "He can hurt the system badly if he wants to. Small countries with high ambitions can't afford to make these kinds of cuts."

Basic researchers are alarmed that Tham is equating funds from the foundations with basic science support from the government research councils. "I'm surprised that our politicians aren't more aware of the difference between research and development," says Gunnar Öquist, head of the research council for the natural sciences. "If all the money shifts to targeted research, the individual scientists with a bright idea is going to find it hard to get funding."

Some Swedish researchers might be able to turn to another source: the European Union (EU). Sweden officially joined the EU on 1 January and now contributes $80 million a year to its science effort. The government expects Sweden's scientists to win back at least that amount in collaborative grants. But first they have to develop their grantsmanship skills. Many Swedes are daunted by the Byzantine application process, or cannot find their areas of interest among those targeted for EU funding, which is also heavily skewed toward strategic research. Torkel Wadström, a medical microbiologist at Lund University, has found half a dozen EU programs that could conceivably fund his research on how bacteria and viruses adhere to cells. But he is spending weeks on grant applications. "Things used to be easy," he says. "You sent in a grant once a year to [one of the research councils]. It took a week to write."

Basic researchers' best hope is that parliament will throw out Tham's plan. The conservatives will oppose it, and academics in Tham's own party are not likely to be supportive. And because the Social Democrats hold only 46% of the seats, Tham will have to muster support from smaller parties to get the simple majority needed to pass the measure. The vote is due in mid-May, and at least until then, coffee-room chat in Swedish labs is as likely to turn to politics as to science.

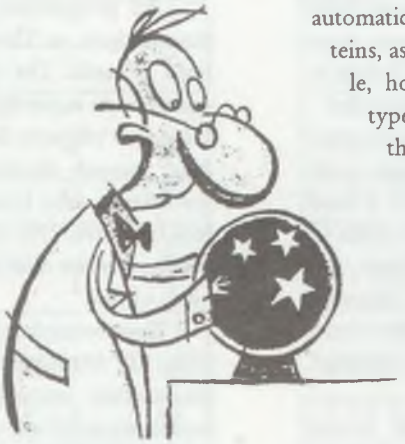
Elizabeth Gardner,
Science, 267 (31 March 1995) 1901

Through the Glass Lightly (Part I)

A collection of scientists at the frontier were asked what they see in the future for science. Here are their views...

If you can look into the seeds of time,
And say which grain will grow and which will not,
Speak then to me, who neither beg nor fear
Your favors nor your hate.

Shakespeare, Macbeth, 1.3.58-61



There will be enormous inroads into human biology and human disease via genomics, gene therapy, and mouse knockout models; a revolution in drug design by combinatorial chemistry; an understanding of the specificity of nerve connections and cognition; and the basic logic of development will be solved (if it is not solved already). New technologies will be developed for studying the structure, function, and dynamics of multiprotein ensembles — for example, the eukaryotic transcription complexes. New methodologies will be developed for studying the behavior of single live cells in isolation or in the context of an embryo. This includes studying the activity of cell itself as well as various subcellular structures.

Hal Weintraub,
Fred Hutchinson Cancer Research Center Seattle, Washington

By the year 2000 or so, the complete genomic sequences of at least five model eucaryotic organisms will be known — *S. cerevisiae, S. pombe, D. melanogaster, A. thaliana*, and *C. elegans* — with substantial information from mouse and humans. Novel sequencing methods will increase the speed of DNA sequencing by a factor of at least 1000. We will also have a complete database of all living organisms, including not only taxonomic data, but also morphological, ecological, biogeographical, and biological data. A complete census of the living organisms in selected habitats will be made.

Michael Ashburner,
Department of Genetics, University of Cambridge

By the end of the decade, all the genes contributing to genetically complex diseases of humans will allow identification of individuals at risk for diabetes, schizophrenia, obesity, and many other diseases. In many cases, disease will be either avoidable by modification of behavior or ameliorated by therapeutic intervention. For societies with socialized health care programs, the economic cost of screening will need to be balanced by the overall savings in disease reduction. If individuals refuse preventive treatment, screening is not cost-effective. For societies with private health care systems, the rich will become healthier and the poor sicker. In both systems, balancing the rights of individuals against the needs of society is going to be difficult.

Peter N. Goodfellow,
Department of Genetics, University of Cambridge

By using techniques involving in vitro fertilization, it is already possible to remove one cell from the developing embryo and characterize any desired region of DNA. Genetic screening of embryos, before implantation, may soon become routine. It will be possible, by sequencing important regions of the mother's DNA, to infer important properties of the egg from which the person develops. This assumes that predictions of protein structure and function will be accurate enough so that one can deduce, automatically, the relevant properties of many important proteins, as well as the regulation of their expression (for example, how much will be made at a particular tissue or cell type) from the sequence of genomic DNA alone. All of this information will be transferred to a supercomputer, together with information about the environment — including likely nutrition, environmental toxins, sunlight, and so forth. The output will be color movie in which the embryo develops into a fetus, is born, and then grows into an adult, explicitly depicting body size and shape and hair, skin, and eye color. Eventually the DNA sequence base will be expanded to cover genes important for traits such as speech and musical ability; the mother will be able to hear the embryo — as an adult — speak or sing.

Harvey F. Lodish,
Whitehead Institute for Biomedical Research Cambridge, Massachusetts

The old phrase "you can't get blood from a turnip" may be proven incorrect, at least partially. Transgenic plants hold promise as biomanufacturing systems for a wide variety of human proteins, including those found in blood plasma. Serum albumin, for instance, has been shown to be expressed and processed correctly when the gene encoding it was introduced into plants. The missing element in this scenario is process technology, which will make it possible to do large-scale protein purification from plant tissues. Advances in high-level protein expression in specialized plant tissues (such as seeds, fruits, or tubers) coupled to engineering improvements in protein isolation may make this technology feasible in the coming decade.

Charles J. Arntzen,
Institute of Biosciences and Technology, Texas A&M University

In the latter half of the 1990s there will be an increasing realization that nature has been constructing transgenic organisms for millions of years. The natural mechanisms of horizontal gene

transfer will be discovered and the consequences will have major impact on the public perception of transgenic organisms and their release into the environment.

For many years the control of insect has stressed eradication. A far better long-term strategy would be to replace a population with one that can do no harm — for example, to replace a population of *Anopheles gambiae*, a major vector of malaria, with one that is unable to transmit the parasite. Three developments are required, all foreseeable with an extension of current technologies: (i) a robust method to transform nondrosophilid insects, (ii) the identification of genes with the required characteristics (for example, that confer on their carriers the inability to transmit a parasite or alter host plant preference of an insect pest), and (iii) the discovery of ways to drive these genes into natural populations (for example, by using transposable elements or symbiotic microorganisms).

Michael Ashburner,
Department of Genetics, University of Cambridge

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There is and will be no truly comprehensive theory of a single mechanism of superconductivity. The basic physics of the phenomenology has been under control for nearly 40 years and is the paradigmatic example of broken symmetry; gauge symmetry broken by condensation of Fermion pairs. It is clear that there are about four (or five if one includes ^{3}He) distinct mechanisms giving pair condensation, of which at least one (the mechanism in ultra-low temperature heavy electron metals such as UBe_{13}) is totally unknown. As for the high critical-temperature cuprates (T_c), a solution is evident, although some minor details remain to be filled in. Five years will certainly be enough for the more general dissemination of that realization and for the more formal working out of the theory's consequences. More difficult is guessing when or whether the long-jam in the theory of metals, which is blocking our understanding of the other cases and many other puzzling phenomena in related fields, will give, if ever.

The question of room-temperature superconductivity is very much a layman's question, since it is the one question no theory of superconductivity will ever answer (just as no theory of liquids can tell you the boiling point of water). The cuprates seem to be going to peak under 200K. The cuprate mechanism could possibly give a higher T_c if there were some (possibly chemically unstable) way in which CuO_2 planes could become even more closely coupled. All of the other hypothetical mechanisms proposed for higher T_c's over the years (bipolarons, excitons, antiferromagnetic spin fluctuations, and so on) are, for one fundamental reason or another, unworkable.

We will come in 20 years to wonder why we cared so much. It is not clear why or whether a room-temperature superconductor would be more useful for most purposes (although it could be a godsend for biological instrumentation). For most uses, advances in cryogenics will make 77 K so easy to manage that little flexibility is lost.

In 20 years a 100-Tesla magnet for scientific uses will exist using currently known materials. By that time power transmission on superconducting wires will occupy some special niches, and experimental fusion reactors will use superconducting magnets with at least partially cuprate windings. Experimental superconducting Maglev trains will exist. SQUID (superconducting quantum interference device) magneto-encephalograms will be a major diagnostic technique. But the real major use of superconductivity will turn out to be something we haven't yet thought of.

P.W. Anderson,
Joseph Henry Laboratories of Physics,
Princeton University

The unexpected discovery of the cuprate family of superconductors which can carry substantial supercurrents at liquid air temperatures (-196°C) has made a room-temperature superconductor conceivable. This new form of superconductivity has an electronic origin, and this makes it more similar to other electronic states such as magnetism, which often set in well above room temperature. A useful room-temperature superconductor, able to support a large supercurrent, will need to have an even higher transition temperature. It is clear that the conditions to realize this new form of superconductivity are restrictive, and considerable ingenuity or luck (or both) will be necessary to synthesize a useful room-temperature superconductor.

T.M. Rice,
AT&T Bell Laboratories,
Murray Hill, New Jersey

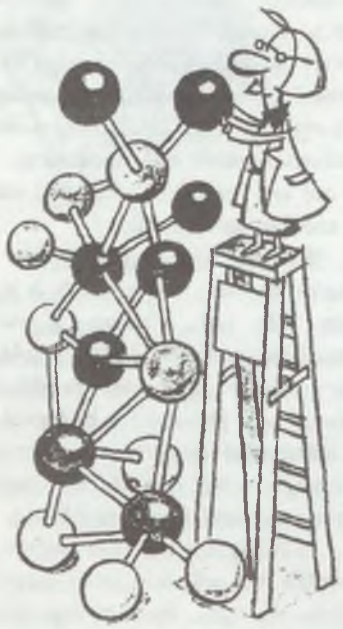
Major benefits for medicine, telecommunications, and electrical power systems will be realized in the near future, based on the high-temperature superconducting cuprates. We expect new medical systems with more powerful, less harmful, and cheaper diagnostics for noninvasive probing of the heart, brain, and body. Clinical tests with arrays of SQUIDs, which are by far the most sensitive detectors of magnetic signals, will replace less informative, riskier, and more costly catheter procedures used to locate the excess electrical currents associated with arrhytmia and other heart malfunctions. In magnetic resonance imaging (MRI) systems, the great improvement in signal-to-noice ratio that superconducting coils in liquid nitrogen have over the copper detector coils will lead to faster and cheaper diagnoses. Similar improvements will

occur in nuclear resonance spectroscopy. MRI will be extended to inexpensive, low magnetic field systems in doctors' offices rather than in hospitals. MRI mammograms, which can replace x-ray scans, will be much more reliable and safer. The development of passive radio-frequency circuits that can handle large amounts of microwave power will result in transmitters and receivers for microwave telecommunications that will double the effectiveness of the limited frequency band that has been allocated by the Federal Communications Commission for such purposes. New strategies such as ion beam-assisted vapor deposition will lead to the manufacture of long lengths of wire and cable needed for the higher temperature, higher field systems. Coaxial superconducting underground power transmission cables, which offer high capacity, no visual pollution, and are relatively inexpensive, will be used to bring more electrical power into our cities.

Theodore H. Geballe,
Department of Applied Physics,
Stanford University

Rational drug design based on structural information is often discussed but seldom realized. The discovery that many important enzymes such as protein kinases, protein phosphatases, and steroid hormone receptors are held inactive by intrasteric inhibition may simulate rethinking. Frequently the intrasteric inhibition, defined as a segment of the protein that blocks its active site, is of the pseudosubstrate type. For example, in protein kinases the inhibitory region can have a primary amino acid sequence similar to that of the substrate, but lacks a residue that can be phosphorylated. Synthetic peptide analogs of these autoinhibitory domains can have affinities for the enzyme that are three orders of magnitude greater than those demonstrated by physiologically relevant substrates. Such proteins are activated by a regulatory protein or by phosphorylation in a signal transduction cascade, leading to removal of the autoinhibitory sequence and providing ready access to the active site. Solving the three-dimensional structure of such proteins in the autoinhibited and active state should allow rational design of peptides or organics that would mimic the pseudosubstrate. Such synthetics should reveal a reasonable degree of specificity and thus could prove to be useful drugs.

Anthony R. Means,
Department of Pharmacology,
Duke University, Medical Center



Rational drug design will be possible in the near term for only a few disorders. While modern technologies make possible the tailoring of compounds to block enzymatic actions, or put defective ligands in unoccupied receptors, the intricacies, interdependencies, and redundancies of human physiology will continue to defy simple pharmaceutical solutions to most diseases. Occasionally the regional drug designers will be lucky, but more often our lack of knowledge of the details, particularly the details of the integration of functions, will lead to ineffective compounds or unacceptable side effects. Rational drug design will be generally successful in the future, but not yet!

The rapid emergence of drug-resistant microbial agents will lead to renewed searches for antibiotics. Common antibiotics were identified by screening natural products — for example, soils and molds. Renewed searches of other natural products will identify one or more "new" classes of agents with new modes of action. Rational drug design may play a role in this search, but whether synthetic or natural products will be identified first is far from clear.

Helen M. Ranney,
Alliance Pharmaceutical Corporation,
San Diego, California

Rational drug design involves determination of the detailed three-dimensional structure of a target protein, such as an enzyme or a cell surface receptor. Molecular modeling is then used to design a small molecule that is expected to bind tightly to the recognition surface of the protein and thereby perturb its biological function. Now, however, in vitro selection techniques coupled with DNA amplification by the polymerase chain reaction allow RNA or DNA ligands to be identified that bind tightly to virtually any protein, without any knowledge of its structure. These methods allow libraries of 10^{14} random nucleic acid sequences to be screened for activity and specificity by a single student in a few weeks or months, as far cry from the 10^5 compounds that can be screened by a large pharmaceutical company in a year. Because it is so fast and dependable, irrational drug design may overshadow rational drug design as the basis for discovering new pharmaceutical leads. Similar principles can be applied to organic synthesis. Miniature biochips allow multiple random reactions to be carried out in a large matrix, which can then be screened for activity and the active compounds identified.

Thomas R. Cech,
Howard Hughes Medical Institute, Boulder, Colorado

Combinatorial chemical libraries will be a major source of new leads for drug development. Not only will the range of libraries be greatly extended, but new automated screening procedures will be developed. Combinatorial algorithms will influence the genetic engineering of microbes for the production of antibiotics and other chemicals. Biologists will screen

commercially available libraries for ligands. Combinatorial chemistry will influence the design of proteins with novel catalytic and biological properties. Novel DNA-binding proteins will be designed at will.

Michael Ashburner
Department of Genetics, University of Cambridge

The marine environment has only recently been explored as a source of new drugs, such as antibiotics and anticancer drugs. Promising drugs, such as curacin-A and bryostatin-1, are undergoing clinical trials. Bryostatin-1, which stimulates the immune system to promote growth of normal bone marrow cells, has been somewhat effective against melanoma, ovarian cancer, and leukemia. Other marine-based drugs should provide a rich complement of new pharmaceuticals. What is not yet clear is whether there are fundamental principles underlying the uniqueness of marine organisms that will permit predictive pathways leading to the development of new anticancer agents and antibiotics.

Rita R. Colwell,
Maryland Biotechnology Institute, Univ. Maryland

Investigators of cancer, inflammation, and other diseases continue to discover rate-limiting biochemical events as targets for useful drugs. Often the ideal drug would block an interaction between two proteins or between a protein and DNA or RNA. The complexity of macromolecular interactions greatly exceeds that of interactions between small ligands or substrates and an allosteric regulatory protein or enzyme. Because peptides or other macromolecules that compete effectively for a targeted binding site are usually poorly suited for oral absorption and penetration across the cell membrane, small molecules are usually more suitable for development as drugs. Recent advances make it possible to produce the relevant macromolecules and to device large-scale assays of their interactions. Such screening assays could efficiently identify the necessary small molecules. Alternatively, three-dimensional mapping of binding interfaces between macromolecules could reveal how to design small molecules that can block the interaction with affinities suitable for developing useful drugs.

Henry R. Bourne
Department of Pharmacology,
University of California, San Francisco

What's hot in ecology/environmental sciences...

Rank	Paper	Citations Through 1993
1	**A.H. Johnson, T.G. Siccama**, "Acid deposition and forest decline," *Env. Sci. Tech.*, 17(7):A294-305, 1983. [U. Pennsylvania, Philadelphia; Yale U., New Haven, Conn.]	213
2	**D.W. Schindler, I.J. Davies, D.R. Cruikshank, D.L. Findlay, J.A. Shearer**, "Long-term ecosystem stress: the effects of years of experimental acidification on a small lake," *Science*, 228(4706):1395-1401, 1985. [Fisheries & Oceans Canada, Winnipeg]	194
3	**N. van Breemen, P.A. Burrough, E.J. Velthorst, H.F. van Dobben, T. de Wit, T.B. Ridder, H.F.R. Reijnders**, "Soil acidification from atmospheric ammonium sulfate in forest canopy throughfall," *Nature*, 299(5883):548-50, 1982. [Agr. U. Wageningen, Netherlands; Res. Inst. Nature Mgmt., Leersum, Netherlands; Royal Meteorol. Inst., De Bilt, Netherlands; Inst. Publ. Hlth., Bilthoven, Netherlands]	182
4	**B.J. Cosby, G.M. Hornberger, J.N. Galloway, R.F. Wright**, "Modeling the effects of acid deposition: Assessment of a lumped parameter model of soil water and streamwater chemistry," *Water Res. R.*, 21(1):51-63, 1985. [U. Virginia, Charlottesville; Norwegian Inst. Water Res., Oslo]	176
5	**B. Nihlgard**, "The ammonium hypothesis: an additional explanation to the forest dieback in Europe," *Ambio*, 14(1):2-8, 1985. [U. Lund. Sweden]	171
6	**S.E. Lindberg, D.W. Johnson, G.M. Lovett, D.D. Richter**, "Atmospheric deposition and canopy interactions of major ions in a forest," *Science*, 231(4734):141-5, 1986. [Oak Ridge Natl. Lab., Tenn.; U. Michigan, Ann Arbor]	152
7	**E.C. Krug, C.R. Frink**, "Acid rain on acid soil: a new perspective," *Science*, 221(4610):520-5, 1983. [Connecticut Agr. Exptl. Stn., New Haven]	152
8	**G.M. Lovett, R.K. Olson, W.A. Reiners**, "Cloud droplet deposition in subalpine balsam fir forest: Hydrological and chemical inputs," *Science*, 218(4579):1303-4, 1982. [Dartmouth Coll., Hanover, N.H.]	142
9	**J.M. Waldman, R.C. Flagan, M.R. Hoffmann, D.J. Jacob, J.J. Morgan, J.W. Munger**, "Chemical composition of acid fog," *Science*, 218(4573):677-80, 1982. [Caltech, Pasadena]	137
10	**J.N. Galloway, G.E. Likens**, "Acid precipitation: the importance of nitric acid," *Atmos. Envir.*, 15(6):1081-5, 1981. [U. Virginia, Charlottesville; Cornell U., Ithaca, N.Y.]	116

SOURCE: ISI's High-Impact Papers, 1981-93

What's hot in chemistry...

Rank	Paper	Citations This Period (Jan-Feb 95)	Rank Last Period (Nov-Dec 94)
1	**B.G. Johnson, P.M.W. Gill, J.A. Pople**, "The performance of a family of density functional methods," *J. Chem. Phys.*, 98(7):5612-26, 1 April 1993. [Carnegie Mellon U., Pittsburg, Penna.]	23	1
2	**K.C. Nicolaou** and 10 others, "Total synthesis of taxol," *Nature*, 367(6464):630-4, 17 February 1994. [Scripps Res. Inst., La Jolla, Calif.; U. Calif., San Diego]	21	5
3	**A.D. Becke**, "Density-functional thermochemistry. III. The role of exact exchange," *J. Chem. Phys.*, 98(7):5648-52, 1 April 1993. [Quenn's U., Kingston, Canada]	20	3
4	**R.A. Holton** and 17 others, "First total synthesis of taxol. 1. Functionalization of the B ring." *J. Amer. Chem. Soc.*, 116(4):1597-8, 23 January 1994. [Florida St. U., Tallahassee]	17	—
5	**S.H. Friedman, D.L. DeCamp, R.P. Sijbesma, G. Srdanov, F. Wudl, G.L. Kenyon**, "Inhibition of the HIV-1 protease by fullerene derivatives. Model building studies and experimental verification," *J. Amer. Chem. Soc.*, 115(15):6509-9, 28 July 1993. [U. Calif., San Francisco; U. Calif., Santa Barbara]	15	—
6	**R.A. Holton** and 17 others, "First total synthesis of taxol. 2. Completion of the C and D rings," *J. Amer. Chem. Soc.*, 116(4):1599-600, 23 January 1994. [Florida St. U., Tallahassee]	14	—
7	**A.D. Becke**, "A new mixing of Hartree-Fock and local density-functional theories," *J. Chem. Phys.*, 98(2):1372-7, 15 January 1993. [Queen's U., Kingston, Ontario, Canada]	14	—
8	**L. Isaacs, A. Wehrsig, F. Diederich**, "Improved purification of C_{60} and formation of σ- and π-homoaromatic methano-bridged fullerenes by reaction with alkyl diazoacetates," *Helv. Chim. A.*, 76(3):1231-50, 12 May 1993. [ETH, Zurich, Switzerland]	9	—
9	**E. Fan, S.A. Van Arman, S. Kincaid, A.D. Hamilton**, "Molecular recognition: Hydrogen-bonding receptors that function in highly competitive solvents," *J. Amer. Chem. Soc.*, 115(1):369-70, 13 January 1993. [U. Pittsburgh, Penna.]	9	—
10	**H. Tokuyama, S. Yamago, E. Nakamura, T. Shiraki, Y. Sugiura**, "Photoinduced biochemical activity of fullerene carboxyl acid," *J. Amer. Chem. Soc.*, 115(17):7918-9, 25 August 1993. [Tokyo Inst. Tech., Japan; Kyoto U., Japan]	9	—

SOURCE: ISI's Hot Papers Database.
NB. Only papers published since January 1993 are tracked. A dash indicates that the paper was not ranked in the Top Ten during the last period. In the event that two or more papers collected the same number of citations in the most recent bimonthly period, total citations to date determine the rankings.

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